CHAPTER 22

CONCLUSIONS

INTRODUCTION

This chapter summarizes the conclusions drawn from the statistical analyses that have been conducted on the Air Force Health Study data base. The followup study, which began in 1985, was the logical extension of the 1982 Baseline study, building upon the strengths of the Baseline study and utilizing the data collected at both the Baseline and the followup. The high level of Government support and outstanding participation of the study subjects that characterized the Baseline study were maintained through this first followup.

STUDY PERFORMANCE ASPECTS

Of the living Baseline study participants, 99.2 percent were located and asked to participate in the followup. Participation in the followup physical examination and questionnaire was very high. Of the fully compliant Baseline participants, 971 of the 1,045 Ranch Hands (92.9%) and 1,139 of the 1,224 Comparisons (93.1%) participated in the followup. Thus, there was no group difference in compliance of the Baseline participants at the followup. Overall, the 2,309 participants in the followup (1,016 Ranch Hands and 1,293 Comparisons) represented a loss of 159 individuals and a gain of 199 since Baseline. One percent of the fully compliant Baseline population died between 1982 and the 1985 followup examination.

The bias/compliance analyses suggested that there had been no change between Baseline and the followup in the way replacements volunteered for entry into the study, and that no additional bias had been introduced at the followup due to scheduling differences. Although replacements were not health-matched at Baseline as they were at the followup, they were similar to refusals with respect to reported health, medication use, and income level. The results supported the use of the total Comparison group in the main analyses presented in this report.

POPULATION CHARACTERISTICS

Overall, the Ranch Hands and Comparisons reported similar social and behavioral characteristics. No significant differences were found in age, educational background, religious preference, current military status, and income level. Significantly more Ranch Hands smoked cigarettes at the time of the followup examination than did Comparisons, but there was no significant difference between groups on past cigarette, cigar, and pipe use and on recent and past use of marijuana. A much higher percentage of participants

reported past marijuana use at the followup than at Baseline. This difference was most likely due to a greater level of confidentiality afforded by the questionnaire technique. Risk taking behavior, assessed by questions on potentially dangerous recreational activities, revealed borderline significance. Slightly more Comparisons were scuba divers and more Ranch Hands raced motor vehicles. The difference in scuba diving was also significant at Baseline.

Patterns of Results

Both the chapter conclusions and the final conclusions of this report have been predicated upon concepts of consistency, specificity, coherence, strength, and plausibility as they apply to the interpretation of group differences. In particular, careful consideration has been given to a variety of data and patterns of results that have emerged from the clinical evaluations. Specifically, there were few differences in the proportions of abnormalities between groups; the positive associations have not aggregated in the clinical areas of prime dioxin concern, nor have they been of serious clinical importance; the unadjusted results have been remarkably concordant with the adjusted results, both in terms of relative risk and p value; the analyses using the Original Comparison set have largely mirrored the results found with the total Comparison group; many of the group differences noted at Baseline have disappeared at the followup examination, and only a few new associations have emerged; almost all of the covariates have acted as expected in the adjusted analyses; and the exposure index analyses and the group-by-covariate interactions have not demonstrated biological patterns of concern and appeared to be more likely due to chance than not. Due to the acknowledged limitations of the exposure index used in this report (and considering the potential use of dioxin body burden levels at the next followup), dose-response relationships have not been emphasized in reaching final conclusions.

The overall pattern of these findings indicates that this followup study cannot be viewed as alarming from the traditional perspectives of clinical medicine or epidemiology. This study, in fact, demonstrates similarity in current health status between the Ranch Hand and Comparison groups.

CLINICAL ASPECTS

General Health

The nonspecific assessment of general health showed relatively close similarity between the two groups. Ranch Hands rated their health as fair or poor more frequently, but this difference was found only in the enlisted groundcrew and not in the officers nor enlisted flyers. The perception of health in both groups had improved since Baseline. Physician-rated appearance of relative age was not found to be significantly different at the followup in contrast to the Baseline finding that a higher percent of Ranch Hands than Comparisons looked younger than their stated age. The categorical analysis of sedimentation rate showed that the Ranch Hands had more abnormalities than the Comparisons. These results were not supported by the continuous analysis of mean sedimentation rates and were opposite to the

Baseline results, which showed that younger Comparisons had elevated sedimentation rates. The categorical analysis of percent body fat showed no significant differences between the two groups, which was consistent with Baseline. However, the continuous analysis found that the Ranch Hands had a significantly lower mean percent body fat using age, race, and occupation as covariates. The detailed exposure analyses revealed no consistent exposure effects, and this result was consistent with the Baseline analysis. No longitudinal difference was found on perception of health. A significant group difference was found over time for the longitudinal analysis of sedimentation rate due to the change in the findings between the two examinations, possibly related to a change in laboratory methodology.

Malignancy

Skin and systemic cancers, both suspected and verified by medical records, showed no significant group differences for the Baseline-followup interval (1982-1985). However, for all neoplasms combined (malignant, benign, and uncertain), a borderline significant excess in the Ranch Hand group was noted in an unadjusted analysis. The analyses of interval cancers revealed group interactions for verified and verified plus suspected basal cell carcinoma and verified plus suspected systemic cancers. Nonsignificant findings were observed for verified and verified plus suspected sun exposure-related cancers. Verified systemic cancers did not differ significantly between groups.

The analyses of lifetime cancer found significant results for verified basal cell carcinoma and verified sun exposure-related skin cancers. Group interactions were noted for systemic cancer categories and for verified plus suspected basal cell carcinoma. The higher rate of basal cell carcinoma in the Ranch Hands versus the Comparisons found at Baseline was nonsignificant for the followup interval, but due to the effect of the larger number of Baseline cases and the significant confounding of average residential latitude, the adjusted analysis of lifetime basal cell carcinoma emerged as statistically significant.

There were several disparities in the distribution of testicular, colon, and smoking-related tumors in the groups. Further, one case of soft tissue sarcoma and one possible lymphoma (both in Ranch Hands) were diagnosed in the interval, balancing the two similar cases found in the Comparison group at Baseline. Considering that the systemic cancer curves are in their early stages for both groups, with perhaps insufficient latency, the cancer results of the followup examination should not be viewed as disturbing, but as cause for continued monitoring.

Neurological Assessment

None of the 27 neurological variables demonstrated a significant group difference, although several variables had relative risks which were greater than one. There was no group difference in reported neurological illnesses for the interval or for a lifetime history. Of the cranial nerve variables, speech and tongue position were marginally significant, with the Ranch Hands at a slight detriment. The analyses of peripheral nerve function showed no significant differences between the Ranch Hands and the Comparisons. In the analysis of central nervous system function, hand tremor was found to be of borderline significance, with the Ranch Hands faring slightly worse than the Comparisons. A borderline significant group interaction (Ranch Hand hand tremor by insecticide exposure) may have had biological and operational

significance. Overall, substantially fewer neurological abnormalities were detected at the followup examination than at the Baseline examination. The exposure analyses showed only occasional statistically significant results, although no consistent pattern with increasing exposure was evident. In the longitudinal analysis of the Babinski reflex, a significant change over time was observed. This was due to a nonsignificant finding in the Ranch Hands at the followup, which differed from the significant adverse finding at Baseline. The covariates of age, alcohol history, and diabetes showed classical effects with many of the neurological measurements. Overall, the followup examination results were quite similar to the Baseline findings.

Psychological Assessment

The reported and verified data on lifetime psychological illnesses showed no significant differences between groups. Distributional tests of the 14 Minnesota Multiphasic Personality Inventory (MMPI) scales, stratified by occupation, revealed that only 2 of the 42 results approached significance. For the total Cornell Medical Index (CMI), separate distributional tests were conducted with stratification by age, race, occupation, education, and current drinking status; a significant difference was found for one statum of each of the covariates. In all cases, the mean of the Ranch Hand distribution was greater than the mean of the Comparisons. The analysis of the 14 MMPI scales showed that there was a significant difference between the two groups for denial and masculinity/femininity, with more abnormalities in the Comparisons than the Ranch Hands. The results of the analyses for hysteria were of borderline significance, with more abnormalities in the Ranch Hands. There were more abnormalities in the Ranch Hands than the Comparisons for social introversion, which was of borderline significance. Differences in the total CMI and A-H area subscore were found to be significant, with more abnormalities in the Ranch Hands. There was no significant difference between the two groups on the Halstead-Reitan Battery impairment index, a measure of the functional integrity of the CNS. The exposure index analyses did not reveal any pattern consistent with a dose-response relationship. As expected, the effects of age, educational level, and alcoholic history showed profound effects on many of the psychological measurements.

Gastrointestinal Assessment

Although the followup gastrointestinal assessment disclosed more statistically significant findings than the Baseline examination, the abnormalities were distributed equally between the two groups, and there was no clinical, statistical, or exposure pattern consistent with an herbicide-related effect on health. No historical or biochemical evidence was found to suggest an increased likelihood of porphyria cutanea tarda (PCT) in the Ranch Hand group. Only sparse and nonsignificant liver disorders were reported for the interval between Baseline and followup. Also, for the lifetime history of liver disorders, there were no significant differences between groups. Further, there were no significant group differences in reported lifetime peptic ulcer disease. A review of digestive system mortality showed a relative excess in the Ranch Hands but a relative lack of malignant neoplasms. The results of the physical examination showed a borderline increase of hepatomegaly in the Ranch Hand group. There was a significantly lower mean serum glutamic-pyruvic transminase (SGPT) level, a greater mean alkaline phosphatase level, and a lower mean uroporphyrin level in the Ranch

Hand group. The analysis of coproporphyrin was of borderline significance, with the mean of the Ranch Hands in excess of the mean of the Comparisons. No group differences were found for serum glutamic-oxaloacetic transminase (SGOT), gamma-glutamyl transpeptidase (GGTP), total and direct bilirubin, lactic dehydrogenase (LDH), cholesterol, or triglycerides. The numerous group-by-covariate interactions did not disclose any consistent subgroup patterns detrimental to the Ranch Hands. These findings were generally consistent with the results of the 1982 assessment. The longitudinal analyses for SGOT, SGPT, and GGTP showed no significant differences between results by group over time.

Dermatological Evaluation

No significant group differences were identified in the dermatological evaluation. None of the questionnaire data showed an increased likelihood of past chloracne, as determined by anatomic patterns of acne, and no cases were diagnosed in the physical examination. Analyses were conducted on six dermatologic disorders (comedones, acneiform lesions, acneiform scars, inclusion cysts, depigmentation, and hyperpigmentation) and on a composite variable of 16 other minor conditions (the latter not generally associated with chloracne). Exposure index analyses did not reveal consistent patterns suggestive of a dose-response relationship. The longitudinal analysis, based on a composite dermatology index, showed no significant differences between the results over time. Substantially more dermatologic abnormalities were detected at the followup examination than at the Baseline examination. In general, however, the followup results were consistent with the findings at Baseline.

Cardiovascular Evaluation

Overall there was general similarity in the cardiovascular health of the Ranch Hands and the Comparisons. Of the 27 cardiovascular variables, there was a significant difference for only one, verified heart disease, with an excess in the Ranch Hand group. This finding was largely unsupported by other cardiac measurements. The cardiovascular assessment was based on reported and verified heart disease; the measurement of central cardiac function by systolic blood pressure, abnormal heart sounds, and ECG findings; and the evaluation of peripheral vascular function by diastolic blood pressure, funduscopic examination, presence of carotid bruits, and detailed manual and Doppler measurements of five peripheral pulses. Doppler recordings of five peripheral pulses were similar in both groups, a finding which was in marked contrast to the Baseline examination that found significant pulse deficits in the Ranch Hand group. This change was most likely due to a required 4-hour abstinence from tobacco prior to the pulse measurements. Overall, the exposure analyses were unsupportive of any meaningful dose-response relationship. The longitudinal analyses confirmed the change in pulse abnormalities in the Ranch Hand group over time, but showed no significant group change in overall ECG findings between the examinations.

Hematological Evaluation

The hematological evaluation found that neither group manifested an impairment of the hematopoietic system, consistent with similar findings at

the Baseline. The evaluation was based on eight peripheral blood variables: red blood cells (RBC), white blood cells (WBC), hemoglobin (HGB), hematocrit concentration (HCT), corpuscular volume (MCV), corpuscular hemoglobin (MCH), corpuscular hemoglobin concentration (MCHC), and platelet count (PLT). Both the discrete and categorical analyses revealed no significant group differences. The covariate effects of age, race, occupation, and smoking history were highly significant for many of the variables. Two group-by-covariate interactions in the analyses of mean differences did not appear to have a meaningful interpretation. The exposure index analyses did not support any plausible dose-response relationship. The longitudinal analyses of MCV, MCH, and PLT found significant differences only for PLT between the Baseline and the followup, with the Ranch Hands exhibiting a slight decline in mean level from Baseline and the Comparisons showing an opposite change.

Renal Assessment

None of the six renal variables of reported kidney disease, urine protein, occult blood, urine white blood cell count, blood urea nitrogen, and urine specific gravity showed a significant difference between the two groups based on the unadjusted analyses. In the adjusted analyses of the laboratory variables, however, there were significant group-by-covariate interactions that did not yield a consistent pattern to suggest a renal detriment to either group. The finding of group equivalence for past kidney disease was in contrast to the Baseline examination, which found significantly more reported disease in the Ranch Hand group. The difference in findings is more likely due to a change in questionnaire wording than to a true change in renal health. Like the Baseline findings, the exposure index analyses showed very little evidence of a dose-response relationship. In the longitudinal analyses of blood urea nitrogen, there was no significant group difference in the change between the examinations.

Endocrine Assessment

In general, the endocrine health status of the Ranch Hands and the Comparisons was reasonably comparable. The examination found no significant differences between the two groups for past thyroid disease, or thyroid and testicular abnormalities determined by palpation. In the analyses of the seven laboratory values (T_3 % Uptake; thyroid stimulating hormone [TSH]; testosterone; initial, second, and differential cortisol; and postprandial glucose), significant differences were found for TSH and testosterone, with higher mean levels in the Ranch Hands. These analyses were not supported by the categorical analyses. The thyroid test results were conflicting with respect to an assertion of hypothyroidism in the Ranch Hands (a possible dioxin effect). Mean levels of testosterone were significantly elevated in the Ranch Hand group as contrasted with the Comparisons in the 10-25 percent body fat category. The effects of personality score and percent body fat on the differential cortisol levels were not fully expected. Although tests of 2-hour postprandial mean values showed no significant group differences, comparable categorical tests revealed that significantly fewer Ranch Hands had impaired glucose levels, but conversely, had more (nonsignificant) diabetic levels of glucose. Analyses of the composite diabetes indicator (history plus 2-hour postprandial results) did not disclose significant group differences. The exposure index analyses suggested that the enlisted flyers in the medium exposure level were significantly different from those in the

low exposure level for differential cortisol, postprandial glucose, and testosterone. The corresponding high to low contrasts were not significant. The longitudinal analyses were based on T_3 % Uptake, TSH, and testosterone, and revealed only symmetrical and nonsignificant changes in the Ranch Hand and Comparison groups over the time interval.

Immunological Evaluation

Overall, there were no significant group differences or any indication of impaired immunological competence in either group based on comprehensive cell surface marker and functional stimulation studies. Six cell surface markers (total T cells, helper T cells, suppressor T cells, B cells, monocytes, HLA-DR cells, and a constructed helper/suppressor ratio variable) and three functional stimulation studies (PHA, pokeweed, and mixed lymphocyte culture) were conducted on 47 percent of the study population. No significant differences were revealed for five of these variables. In the analyses of the other five variables, there were significant group-by-covariate interactions, but no discernible pattern was identified to suggest a detriment in any subgroup of either group. Skin test assessments of delayed hypersensitivity were characterized by inter-reader variation and shifting diagnostic criteria for anergy. The skin test data were judged invalid and were not subjected to statistical testing for group differences. No consistent pattern of immunological deficits could be associated with increasing levels of herbicide exposure in the Ranch Hand group.

Pulmonary Disease

The pulmonary assessment did not reveal any statistically significant differences between the Ranch Hand and Comparison groups that were suggestive of an herbicide-related disease. The analyses consisted of group assessments of respiratory disease incidence, physical examination abnormalities, and the current prevalence of x-ray abnormalities. There were no significant differences between the Ranch Hands and Comparisons for history of asthma, bronchitis, pneumonia, or for six of seven clinical variables (excluding rales) determined by x-ray or auscultation. Analyses of history of pleurisy, history of tuberculosis, and rales showed significant but inconsistent group-by-covariate interactions. These findings did not indicate any patterns suggesting a different disease experience in the two groups. The exposure index analyses did not reveal any consistent pattern suggestive of an increasing dose response.

CONCLUSION

The results of the first followup study in 1985 have shown a subtle but consistent narrowing of medical differences between the Ranch Hands and Comparisons since the Baseline Study in 1982. The 1985 examination results provide reassuring evidence that the current state of health of the Ranch Hand participants is unrelated to herbicide exposure in Vietnam. Continued close medical surveillance of these military populations is strongly indicated. This followup report concludes that there is not sufficient plausible or consistent scientific evidence at this time to implicate a causal relationship between herbicide exposure and adverse health in the Ranch Hand group.